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Substituent Effects and Additivity in the Carbon-13 Nuclear Magnetic Resonance Spectra of Chlorinated Naphthalenes and Their Chlorinated Naphthol Metabolities

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Substituent Effects and Additivity in the Carbon-13 Nuclear Magnetic Resonance Spectra of Chlorinated Naphthalenes and Their Chlorinated Naphthol Metabolites

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Carbon-13 and proton nuclear magnetic resonance spectra were obtained for 12 chlorinated naphthalenes and six chlorinated naphthols, some of which are metabolites of the naphthalenes. The validity of the use of additivity of chlorine and hydroxyl substituent effects to predict ^{13}C chemical shifts in these compounds was examined. Deviations from the additivity predictions resulted from peri and ortho substituent interactions, both steric and hydrogen bonding. Despite these deviations, additive substituent parameters could be used to assign ^{13}C spectra correctly and to distinguish uniquely between similar isomers.

Polychlorinated naphthalenes are widely used industrially as complex mixtures of chlorinated naphthalene isomers. Because of the large volume and wide distribution of their use, the potential human exposure to these compounds is great. Characterization of the metabolites and elucidation of the metabolic pathways for chlorinated naphthalenes have been the focus of several investigations in the past few years. Recent work has shown that some individual chlorinated naphthalene isomers are metabolized to chlorinated naphthols.[1,2]

Our interest centered on the identification and characterization of the individual chlorinated naphthalenes and their known and potential metabolites. We were particularly interested in those characteristics which might influence the metabolism or toxicity of these compounds. For example, their steric properties may influence the rate at which hydroxylation takes place. Intramolecular hydrogen bonding in the metabolites may affect the relative rates of excretion and hence the relative toxicities.

Several studies of substituent effects on the ^{13}C shieldings of aromatic compounds have appeared in the literature. Substituent effects in monosubstituted benzenes[4] and halobenzenes[4,5] have been examined. Carbon-13 NMR substituent effects in 4-substituted biphenyls,[6] 4,4'-disubstituted biphenyls,[7] and polychlorinated biphenyls[7,8] have also been studied. Substituent effects on the ^{13}C shieldings of methylnaphthalenes,[9,10] halonaphthalenes,[11,12] and some other naphthalenes[13,14] have been reported. Kitching et al.[15] have analyzed ^{13}C chemical shift data for a large number of 1- and

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2-substituted naphthalenes, in terms of the Taft dual substituent parameter equation, to probe the nature of the transmission of substituent effects in these systems.

Additivity of substituent effects for a single type of substituent, for example, methyl or chlorine, has been used successfully to predict the ^{13}C chemical shifts of the compounds in some of these studies. The exceptions appear to be for compounds in which significant steric interference between the substituents may occur, as in ortho,ortho'-disubstituted biphenyls[8] and 1,8-disubstituted naphthalenes.[10,12] For example, in the halonaphthalenes[12] good agreement with additivity predictions was observed for 1,5- and 2,7-X_2-naphthalenes (X = F, Cl, or Br), but large deviations from the predicted chemical shift values were observed for 1,8-X_2-naphthalenes.

Our objectives in this study were fourfold: first, to obtain ^{13}C NMR parameters for individual chlorinated naphthalenes and their hydroxylated metabolites;[16] second, to test the validity of the assumption that substituent effects on ^{13}C shieldings are additive for naphthalenes with multiple chlorine and hydroxyl substitution; third, to examine the effects of intramolecular steric and hydrogen bonding interactions on the ^{13}C shieldings; and fourth, to determine how well additivity predictions work in uniquely identifying particular isomers without resorting to complete and unequivocal assignment of the ^{13}C spectra.

Experimental Section

Materials. Reagent quality samples of 1-chloro-, 2-chloro-, 2,7-dichloro-, 1,2,3,4-tetrachloro-, and 1,2,3,4,5,6,7,8-octachloronaphthalene, and 1-chloro-4-hydroxynaphthalene were obtained commercially. The dichloronaphthol metabolite of 2,6-dichloronaphthalene was provided by Dr. Ih Chu.[2] The remaining naphthalenes were synthesized in these laboratories by the following methods. The purity and identity of all the naphthalenes synthesized were confirmed by gas chromatography-mass spectrometry, infrared spectroscopy, and melting point measurements.

1,2-Dichloronaphthalene. 1,2-Dichloronaphthalene was prepared from 2-amino-1-nitronaphthalene (Aldrich) by the method of Clemo et al.[17] and purified by column chromatography on silica gel to give mp 34 °C (lit. mp 35 °C).

1,5-Dichloronaphthalene. 1-Amino-5-nitronaphthalene (Aldrich; 2.0 g, 10.6 mmol) was reduced by heating for 6.5 h on a steam bath with iron powder (Alfa Products; 325 mesh; 6.62 g, 0.118 g-atom), water, and a few drops of concentrated hydrochloric acid.[18] The mixture was cooled and extracted with ethanol. The extract was filtered and evaporated to dryness with a rotary evaporator. The resulting diamine was dissolved in 10 mL of 50% concentrated hydrochloric acid, cooled in an ice bath, and tetrazotized with sodium nitrite (1.538 g, 22.3 mmol) in 5 mL of water. The diazonium salt was decomposed by stirring it with a boiling solution of copper(I) chloride (2.62 g) in concentrated hydrochloric acid for 2.5 h. Water was added and the mixture was extracted with benzene. The organic layer was washed with 10% potassium hydroxide solution, water, and saturated sodium chloride and dried over anhydrous sodium sulfate. The solution was filtered and evaporated to dryness on a rotary evaporator, and the residue was purified by column chromatography on silica gel to yield 328 mg (15.7%) of 1,5-dichloronaphthalene, mp 105.5–106 °C (lit.[19] mp 105–107 °C).

1,4-Dichloronaphthalene. 1,4-Dichloronaphthalene was prepared by diazotization of 1-amino-4-chloronaphthalene (Aldrich) followed by decomposition of the diazonium salt in copper(I) chloride in hydrochloric acid. The crude product was purified by column chromatography on silica gel (Woelm, activity grade 1), eluting with hexane. Gas chromatographic analysis indicated a purity of greater than 99%. The compound had mp 66.5–67.5 °C (lit.[20] mp 67–68 °C).

1,8-Dichloronaphthalene. 1-Chloro-8-nitronaphthalene (Aldrich) was reduced with iron powder by the procedure described previously for 1-amino-5-nitronaphthalene. The resulting amine was diazotized, followed by decomposition of the diazonium salt with copper(I) chloride in hydrochloric acid. The product was extracted and purified as in the preceding procedures to yield 123 mg (17.1%) of 1,8-dichloronaphthalene with a purity of 98% by gas chromatography and mp 85–86.5 °C (lit. mp 83[21] and 88 °C[22]).

2,6-Dichloronaphthalene. 2,6-Dichloronaphthalene was prepared from the disodium salt of 2,6-naphthalenedisulfonic acid (Aldrich) and phosphorus pentachloride according to the method of Beattie and Whitmore,[23] mp 134.5–136.5 °C (lit. mp 136 °C). Purity by gas chromatography was better than 99%.

1,2,3-Trichloronaphthalene. 1,2-Dichloro-3-nitronaphthalene (Aldrich) was reduced with iron powder as described previously. The resulting amine was diazotized, followed by decomposition of the diazonium salt with copper(I) chloride in hydrochloric acid. After purification, a white solid, mp 75–77 °C (lit.[24] mp 81 °C), was obtained. The purity of the 1,2,3-trichloronaphthalene was greater than 91% by gas chromatography. Combined GC–MS confirmed the major component as the trichloronaphthalene; the minor component was a dichloronaphthalene.

2-Chloro-1-naphthol and 1-Chloro-2-naphthol. 2-Chloro-1-naphthol and 1-chloro-2-naphthol were prepared from 1-naphthol and 2-naphthol, respectively, by reaction with *tert*-butyl hypochlorite as described by Ginsberg:[25] 2-chloro-1-naphthol, mp 62–63.5 °C (lit. mp 64–65 °C); 1-chloro-2-naphthol, mp 68–70 °C (lit. mp 71 °C).

1-Chloro-8-naphthol. The procedure of Woroshtzow and Koslow[26] was attempted without success. Likewise, diazotization of 1-amino-8-chloronapthalene[18] followed by addition of the diazonium salt to boiling sulfuric acid was unsuccessful as a synthesis for 1-chloro-8-naphthol. The procedure used to synthesize this compound successfully is as follows.

1-Amino-8-chloronaphthalene (400 mg) and 6 mL of 6 M sulfuric acid were sealed in a thick-walled glass tube and kept at 200 °C for 16 h. The tube was broken open and the contents were extracted with benzene. The organic layer was washed with 5% aqueous sodium hydroxide. The aqueous layer was then acidified and extracted with benzene. The extract was washed with water and a saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated to yield 226 mg of crude chloronaphthol. This residue was chromatographed on silica gel to yield 200 mg of pure (99.6% by gas chromatography) 1-chloro-8-naphthol, mp 65–66 °C (lit.[26] mp 65–66 °C).

Anal. Calcd for $C_{10}H_7ClO$: C, 67.24; H, 3.95; Cl, 19.85. Found: C, 67.09; H, 3.93; Cl, 19.99.

Spectral Analyses. Samples. Samples for NMR analysis were 10% w/v solutions in chloroform-*d* (Merck Isotopes) with approximately 0.5% added tetramethylsilane (Me_4Si). The samples were contained in 5 mm NMR tubes.

Spectra. Both ^1H and ^{13}C NMR spectra were recorded on a Varian XL-100 spectrometer with a Nicolet TT-100 Fourier transform system. Proton spectra at 270 MHz were obtained on the Bruker HX-270 superconducting NMR system at Florida State University. Natural abundance ^{13}C NMR spectra were obtained with 5 kHz spectral widths and 16K Fourier transforms at approximately 40 °C. The ^1H noise-decoupled ^{13}C spectra were obtained with a decoupler power of 10 W (reflected power less than 0.5 W) and a noise band width of 1.8 kHz. For selectively decoupled ^{13}C spectra the ^1H decoupler power was low, ca. 100–105 dB on the XL-100 spectrometer, and was set at the proper single frequencies for each individual proton resonance in turn. These frequencies were determined by analyses of the ^1H spectra. Mass spectra were obtained by gas–liquid chromatography and 70 eV electron impact mass spectrometry on a Hewlett-Packard 5930 mass spectrometer with a Hewlett-Packard 5700 gas chromatograph. Infrared spectra were obtained on a Perkin-Elmer 257 grating infrared spectrophotometer.

Proton Spectra. Proton spectra of 1,4-, 1,5-, 1,8-, 2,6-, and 2,7-dichloronaphthalene, and 1,2,3,4-tetrachloronaphthalene were analyzed with the aid of the iterative spectral fitting program LAOCOON III.[27] For 1- and 2-chloronaphthalene the partial assignments of Ernst[12] were used. The remaining ^1H spectra were partly assigned by standard techniques.

Carbon Spectra. Carbon-13 spectra were first obtained with proton noise decoupling to measure the individual ^{13}C chemical shifts. Definitive assignments of most of the hydrogen-bearing carbon resonances were made by selective decoupling. For naphthalenes whose ^1H spectra were only partially assigned, for example, 1- and 2-chloronaphthalene, the ^{13}C spectra of their symmetrically disubstituted counterparts, e.g. 2,7-dichloronaphthalene, and the data of Ernst[12] were used as guides. Additional information was obtained from the proton-coupled ^{13}C spectra. These spectra allowed recognition of the number of vicinal protons and their relationship to a given ^{13}C nucleus.

Quaternary carbon resonances were additionally challenging. Those carbons directly bonded to chlorine or hydroxyl groups have characteristic chemical shifts. Resonances of the hydroxyl-substituted carbons and carbons ortho to them were broadened and shifted slightly in the presence of tris(acetylacetonato)chromium(III).

Table I. Proton NMR Parameters for Some Chlorinated Naphthalenes and Napthols

Naphthalene substitution	Chemical shifts, δ								
	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	OH
2-Cl[a]	7.8–7.9		7.42	7.8–7.9	7.8–7.9	←7.48–7.55→		7.8–7.9	
1,2-Cl_2			←7.38–7.81→					8.22	
1,4-Cl_2		7.428	7.428		8.207	7.571	7.571	8.207	
1,5-Cl_2		7.590	7.439	8.181		7.590	7.439	8.181	
1,8-Cl_2		7.601	7.333	7.727	7.727	7.333	7.601		
2,6-Cl_2	7.757		7.411	7.642	7.757		7.411	7.642	
2,7-Cl_2	7.630		7.346	7.655	7.655	7.346		7.630	
1,2,3,4-Cl_4					8.286	7.649	7.649	8.286	
1-Cl,2-OH			7.21	←7.30–7.74→				8.00	5.89
1-Cl,4-OH		7.364	6.708		8.15–8.25	←7.41–7.74→		8.15–8.25	4.98
1-Cl,8-OH		7.380	7.277	7.718	7.39	7.39	7.034		8.10
2-Cl,1-OH			←7.45–7.56→		8.23	7.75	7.75	8.23	6.00
1,6-Cl_2,2-OH[b]			7.44	7.84	7.98		7.62	8.16	
2,4-Cl_2,1-OH			7.497		8.17–8.22	←7.54–7.65→		8.17–8.22	5.95

Naphthalene substitution	Coupling constants, Hz									
	$J_{1,3}$	$J_{1,4}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{5,6}$	$J_{5,7}$	$J_{5,8}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$
1,4-Cl_2						8.6	1.3	0.6	6.9	1.3	8.6
1,5-Cl_2			7.6	0.6	8.4				7.6	0.6	8.4
1,8-Cl_2			7.6	1.2	8.1	8.1	1.2		7.6		
2,6-Cl_2	2.0	0.1			8.8		2.0	0.1			8.8
2,7-Cl_2	1.9	0.0			8.5	8.5		0.0		1.9	
1,2,3,4-Cl_4						8.6	1.1	0.1	6.5	1.1	8.6
1-Cl,4-OH			8.1								
1-Cl,8-OH			7.9	1.2	8.3						
1,6-Cl_2,2-OH[b]					9.5		2.5				9.0

[a] From ref 12. [b] From ref 2.

Table II. ^{13}C Chemical Shifts (δ) of Chlorinated Naphthalenes and Naphthols[a]

Substitution	Registry no.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1-Cl	90-13-1	131.92	126.09	125.67	(127.12)	128.16	(126.96)	(126.65)	124.41	130.81	134.58
2-Cl	91-58-7	126.57	131.55	126.72	129.47	127.77	126.09	127.04	126.88	134.03	131.63
1,2-Cl_2	2050-69-3	129.38	(131.72)	126.63	128.14	(127.86)	(127.19)	(127.71)	124.57	(130.33)	132.60
1,4-Cl_2	1825-31-6	130.92	125.87	125.87	130.92	124.96	127.74	127.74	124.96	131.63	131.63
1,5-Cl_2	1825-30-5	131.91	127.02	126.66	123.70	131.91	127.02	126.66	123.70	132.27	132.27
1,8-Cl_2	2050-74-0	130.43	130.78	126.05	128.48	128.48	126.05	130.78	130.43	127.46	137.18
2,3-Cl_2	2050-75-1	127.02	(130.11)	(130.11)	127.02	126.85	128.78	128.78	126.85	(132.28)	(132.28)
2,6-Cl_2	2065-70-5	126.54	(131.97)	127.89	128.58	126.54	(131.97)	127.89	128.58	(132.21)	(132.21)
2,7-Cl_2	2198-77-8	125.67	132.81	127.01	129.24	129.24	127.01	132.81	125.67	134.50	129.77
1,2,3-Cl_3	50402-52-3	129.35	130.38	131.41	127.27	127.27	(127.91)	(127.67)	124.81	130.05	132.04
1,2,3,4-Cl_4	20020-02-4	130.12	130.33	130.33	130.12	125.39	128.73	128.73	125.39	129.96	129.96
1,2,3,4,5,6,7,8-Cl_8	2234-13-1	128.74	135.01	135.01	128.74	128.74	135.01	135.01	128.74	129.42	129.42
1-Cl,2-OH	633-99-8	113.37	149.40	117.24	128.19	128.40	124.10	127.54	122.75	131.11	129.52
1-Cl,4-OH	604-44-4	123.57	125.74	108.65	150.57	122.10	126.02	127.58	124.49	131.63	125.50
1-Cl,8-OH	65253-31-8	127.18	127.45	125.40	128.61	120.90	127.63	113.14	152.81	119.84	137.03
2-Cl,1-OH	606-40-6	147.12	113.58	(126.07)	122.16	127.60	(126.66)	125.85	120.93	124.55	133.33
1,6-Cl_2,2-OH	65253-32-9	113.52	149.67	118.51	124.59	127.54	130.12	128.39	126.90	129.54	130.06
2,4-Cl_2,1-OH	2050-76-2	146.37	112.66	125.44	(124.93)	124.44	127.66	126.85	122.51	(123.41)	130.25

[a] Similar values in parentheses may be interchanged.

The relative intensities of the quaternary carbon resonances are influenced by the degree of carbon–hydrogen dipole–dipole relaxation. The efficiency of this relaxation depends on the C–H internuclear distance, r, as $1/r^6$. Carbons with no nearby protons tend to have longer spin lattice relaxation times and smaller nuclear Overhauser enhancements (NOEs) under conditions of proton noise decoupling than do carbons with nearby protons. Hence, the carbons without nearby protons tend to have less intense resonances.

With selective proton decoupling, selective intensity increases of the resonances of nearby quaternary carbons can be observed. These intensity increases may be due entirely to NOEs. They may also be due to removal of small long-range couplings to the proton being irradiated. For example, in 1,5-dichloronaphthalene a selective intensity increase in the C-9,10 resonance was observed when the protons nearest C-9 and C-10, H-4 and H-8, were irradiated. The C-9,10 resonance increased in intensity by 50% relative to the intensity of the C-1,5 resonance.

After application of the assignment techniques above, those few carbon resonances remaining without explicit assignments were assigned to give mutual consistency in the ^{13}C chemical shifts for the entire series of chlorinated naphthalenes and naphthols.

Results and Discussion

Chlorinated Naphthalenes. NMR Parameters. Proton chemical shifts and coupling constants for the compounds studied are given in Table I. Carbon-13 chemical shifts are given in Table II.

Substituent Effects. To derive parameters describing the effects of a 1-chlorine or a 2-chlorine substituent on the ^{13}C chemical shifts of naphthalene, ^{13}C chemical shifts for six chlorinated naphthalenes were used. These naphthalenes all lack significant chlorine–chlorine steric interactions; that is,

Table III. Chlorine and Hydroxyl Substituent Effects (ppm) on the ^{13}C Chemical Shifts of Naphthalene

Substituent	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1-Cl	3.99	0.30	0.04	−0.85	0.23	1.12	1.03	−3.08	−2.58	1.19
2-Cl	−1.23	5.92	0.95	1.77	0.07	0.46	1.34	−0.89	0.66	−1.75
1-OH[a]	23.36	−16.99	0.06	−7.08	−0.16	0.67	−0.47	−6.38	−9.12	1.26
2-OH[a]	−18.26	27.57	−8.00	2.04	−0.05	−2.08	0.80	−1.44	1.15	−4.45

[a] From ref 13a.

Table IV. Differences between Predicted and Observed ^{13}C Chemical Shifts[a] in Some Substituted Naphthalenes

Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1,2-Cl_2	−1.08	−0.1	0.04	−0.48	−0.14	0.01	−0.26	0.84	−1.05	−0.14
1,8-Cl_2	1.82	3.85	−0.71	1.40	1.40	−0.71	3.85	1.82	−0.68	1.50
2,3-Cl_2	−1.22	−2.36	−2.36	−1.22	0.03	1.38	1.38	0.03	1.07	1.07
1,2,3-Cl_3	−2.88	−2.39	−1.10	−0.12	0.16	−0.61	−0.76	1.01	0.42	−1.36
1,2,3,4-Cl_4	−1.26	−2.48	−2.48	−1.26	1.36	−0.82	−0.82	1.36	−0.86	−0.86
1,2,3,4,5,6,7,8-Cl_8	2.29	0.73	0.73	2.29	2.29	0.73	0.73	2.29	1.94	1.94
1,2-Me_2[b]	−2.1	−3.2	1.2	0.1	0.2	−0.2	−0.0	−0.1	0.0	0.5
1,8-Me_2[b]	5.1	3.0	−0.2	1.0	1.0	−0.2	3.0	5.1	1.2	1.7
2,3-Me_2[b]	1.2	−2.3	−2.3	1.2	−0.5	−0.1	−0.1	−0.5	0.6	0.6
1-Cl,2-OH	−0.06	−4.07	−0.40	−0.70	0.52	−0.54	0.11	−0.43	−0.76	−0.52
1-Cl,4-OH	−1.04	−0.22	0.00	0.36	0.55	−0.23	0.28	0.03	−0.35	0.13
2-Cl,1-OH	−2.71	−0.95	−0.54	−1.46	−0.01	−0.07	−0.62	1.73	−0.29	0.52
2,4-Cl_2,1-OH	−2.61	−1.91	−1.47	−1.45	−0.09	−0.10	−0.74	1.85	−2.62	0.02
1-Cl,8-OH	1.87	1.83	−0.94	1.65	−0.18	0.61	3.48	4.83	−1.76	1.28

[a] Observed − predicted values are given in ppm. [b] From ref 10.

they lack ortho or peri disubstitution. Additivity of chlorine substituent effects was assumed. A set of parameters which describes the effects of a 1- or 2-chlorine substituent was derived. The resulting "best fit" parameters give the smallest average deviation between the observed and the predicted ^{13}C chemical shifts assuming additivity. These parameters are given in Table III. They are in good agreement with those reported by Ernst[12] for a smaller set of compounds in a different solvent.

As an example of the use of these parameters, to predict the ^{13}C chemical shift of C-8 in 1,4-dichloronaphthalene the chemical shift of this carbon in naphthalene itself is used, δ 127.74. Add to this −3.08 ppm for the effect of the 1-chlorine at the 8 position. Then add 0.23 ppm for the effect of the 4-chlorine to get a predicted chemical shift for C-8 of δ 124.89. The observed value is δ 124.96, only 0.07 ppm greater than the predicted value.

For the six nonhindered chlorinated naphthalenes, the average deviation for 41 independent positions was only 0.09 ppm.

It is interesting that the effects of a chlorine substituent are substantial, even in the unsubstituted ring. This phenomenon has been observed previously in other systems, for example, in chlorinated biphenyls[7] where a significant substituent effect is transmitted through as many as eight covalent bonds.

In chlorinated naphthalenes where there is steric crowding of the chlorine substituents there are deviations from the ^{13}C chemical shifts predicted by additivity. The deviations observed for several chlorinated naphthalenes are given in Table IV.

Where the chlorines are ortho, as in 1,2- and 2,3-dichloro-, 1,2,3-trichloro-, and 1,2,3,4-tetrachloronaphthalene, steric crowding leads to increased shielding of the carbons in the substituted ring. Increased shielding of closely lying carbons separated by three bonds and the other carbons associated with the crowded part of the molecule has been observed in many systems.[10,28,29] Steric crowding of other substituents separated by three bonds appears to have a similar effect on the associated carbons.

Chlorine has been shown to shield a γ-gauche carbon to approximately the same extent as a methyl group in some monochlorocyclohexanes.[30] Likewise, the increased shielding of the β-carbon, resulting from the γ-gauche interaction, is approximately the same for a chlorine (−3.73 ppm) as for a methyl (−3.62 ppm) substituent on cyclohexane. Comparison of the deviations from additivity for C-2 and C-3 in 2,3-dimethyl- and 2,3-dichloronaphthalene, −2.3 and −2.36 ppm, respectively, suggests that a similar situation exists in aromatic systems. The results for dichloro steric interactions in aromatic systems suggest the need to reinterpret these steric effects without employing a model dependent on nonbonded hydrogen–hydrogen interactions. Recently, Beierbeck and Saunders[31] have suggested the need for such reinterpretation in alicyclic compounds.

Carbons in the unsubstituted ring of the ortho-chlorine-substituted naphthalenes are deshielded at the α positions (C-5 and C-8) but are shielded at the β positions (C-6 and C-7) relative to the predicted values. Octachloronaphthalene is the only exception; all of its carbons are less shielded than predicted.

The magnitudes of the deviations from additivity for the carbons in the crowded part of the molecule appear to be about the same for ortho chlorine and methyl substituents. However, in the unsubstituted ring the effects of ortho methyl interactions are not as large as those of chlorine interactions. Although methyl and chlorine substituents are often considered to have the same steric requirements, the greater ease of distortion of methyl groups may result in less distortion of the overall ring geometry by methyl than by chlorine interactions.

As with ortho disubstitution, the effects of peri disubstitution are large at all positions. Unlike the ortho case, however, the substituted carbons in 1,8-dichloronaphthalene are *deshielded*, as they are in 1,8-dimethylnapthalene. The effect at C-9 of the peri interactions is opposite for the chloro and the methyl compounds. This may reflect greater distortion of the substituted part of the molecule with greater opening of the Cl–C-1–C-9 angle in the chloro compound.[12]

Chlorinated Naphthols. When individual chlorinated naphthalene isomers are administered to pigs or to rats they

Table V. Observed and Predicted ^{13}C Chemical Shifts [a] for a Chloronaphthol

	δ_C observed	δ_C predicted for 1-Cl,2-OH	Observed − predicted	δ_C predicted for 2-Cl,1-OH	Observed − predicted
Quaternary carbons	147.12	*153.47*	−6.35	*149.83*	−2.71
	133.33	131.87	1.46	132.84	0.49
	124.55	*130.04*	−5.49	*124.84*	−0.29
	113.58	113.43	0.15	114.53	−0.95
CH carbons	127.60	128.89	−1.29	127.61	−0.01
	126.66	127.88	−1.22	126.73	−0.07
	126.07	127.43	−1.36	126.61	−0.54
	125.85	124.64	1.21	126.47	−0.62
	122.16	123.18	−1.02	122.39	−0.23
	120.93	*117.64*	3.29	*120.43*	−0.50

[a] Observed − predicted values are given in ppm.

are converted to chlorinated naphthols. Generally, the major metabolites are hydroxylated at the α positions (1,4,5, or 8). There are a few exceptions; for example, 2-chloronaphthalene is metabolized to 2-chloro-3-hydroxynaphthalene.[1] Since the α position is usually preferred, however, most of the chlorinated naphthols which we examined are α-naphthols.

Substituent Effects. To predict the effects of hydroxyl substituents on the ^{13}C shieldings of chlorinated naphthalenes we used the changes in the ^{13}C chemical shifts of naphthalene produced by a 1- or 2-hydroxyl substituent. Since our measured values of these changes agreed with those of Ernst,[13a] we have used his values. These values are given in Table III.

The effects of a hydroxyl substituent are very large, particularly the deshielding of the hydroxyl-substituted carbon and the increased shielding of the carbons ortho and para to it. Because these effects are so large they nearly dominate the ^{13}C shieldings of the chlorinated naphthols.

To predict the ^{13}C chemical shifts of the chlorinated naphthols the additivity of chlorine and hydroxyl substituent effects was assumed. The deviations of the observed from the predicted chemical shifts are given in Table IV.

In 1-chloro-4-hydroxynaphthalene no steric interaction occurs between the substituents. The observed ^{13}C chemical shifts for this compound are reasonably close to the predicted values, except at C-1 and C-5. At C-1 the deviation from additivity of −1.04 ppm may result from hydrogen bonding of the para hydroxyl group, which would markedly change the electron density at C-1. The deviation of 0.55 ppm at C-5 results from a peri interaction with the 4-OH group.

For all the chlorinated naphthols an OH substituent results in increased shielding of the carbon para to the OH. The increase over that predicted by additivity has a mean value of −1.12 ppm with a smaller increase for a β than for an α hydroxyl.

The second chlorinated naphthol, 1-chloro-2-hydroxynaphthalene, has a marked increase in shielding, −4.07 ppm, over the additivity prediction at the OH-substituted carbon. There are smaller shielding increases at positions meta, −0.76 and −0.70 ppm, and para, −0.52 ppm, to the hydroxyl. It is likely that intramolecular hydrogen bonding to the ortho chlorine accounts for most of the deviations from additivity in this compound.

In 1-hydroxy-2-chloro- and 1-hydroxy-2,4-dichloronaphthalene there are large deviations from additivity at all carbons in the substituted ring and at C-8. All deviations except that for C-8 reflect increased shielding. Since the unsubstituted ring shows only small deviations from additivity, except for C-8, significant geometric distortion of the molecule is probably not responsible for the differences from the predicted chemical shifts. Either a 2-chlorine or a 1-hydroxyl substituent by itself leads to increased shielding of C-8. With intramolecular hydrogen bonding and steric interactions between the two substituents, the shielding of C-8 is decreased by almost 2 ppm.

The peri-substituted chloronaphthol in this study, 1-chloro-8-hydroxynaphthalene, exhibits deviations from the additivity predictions which are quite different from those of the other chloronaphthols. As in 1,8-dichloro- and 1,8-dimethylnaphthalene, the peri substitution leads to deshielding of C-1 and C-8. The chlorine-substituted carbon is deshielded to the same extent in both 1,8-dichloronapthalene and 1-chloro-8-hydroxynaphthalene, 1.82 and 1.87 ppm, respectively. The hydroxyl carbon in 1-chloro-8-hydroxynaphthalene is deshielded by 4.83 ppm, in marked contrast to the increased shielding, −2.71 and −2.61 ppm, of this carbon in 2-chloro-1-hydroxy- and 2,4-dichloro-1-hydroxynaphthalene. Perhaps the greater separation of the substituents in the peri compounds, relative to the ortho compounds, leads to reduced intramolecular hydrogen bonding. The reduced shielding seems more characteristic of a peri steric interaction than intramolecular hydrogen bond formation.

Use of Additivity Predictions. To assign all the resonances in a ^{13}C spectrum unequivocally often requires many lengthy separate experiments, such as selective deuteration and selective proton decoupling. Unfortunately, the amount of material available, particularly in metabolism studies, is usually small, 1 mg or less. This increases the required experimental time beyond that available to most researchers. To surmount this problem can we rely on additivity predictions to interpret the ^{13}C spectra of similar isomers which are indistinguishable by other nondestructive means?

As a test of the utility of additivity predictions in distinguishing closely similar isomers, a comparison was made between these predictions for 1-chloro-2-hydroxy- and 2-chloro-1-hydroxynaphthalene, whose gas chromatographic data and infrared, ^1H NMR, and mass spectral characteristics are insufficient to characterize the two isomers uniquely. The ^{13}C chemical shifts were divided into two groups, those for quaternary and those for protonated carbons, which are readily ascertained from the ^1H noise-decoupled ^{13}C spectrum. The chemical shifts predicted using the hydroxyl and chlorine substituent parameters in Table III were then listed in order of decreasing frequency for each group. These were compared with a similar list obtained from the experimental ^{13}C spectrum (for 2-chloro-1-hydroxynaphthalene). The results of comparisons of these lists are given in Table V. The mean deviation between the observed and the predicted chemical shifts is 2.28 ppm for a 1-Cl,2-OH structure, but only 0.64 ppm for a 2-Cl,1-OH structure. If a reasonable agreement of ±1 ppm is required, all shifts except one predicted for a 2-Cl,1-OH structure agree with those observed, whereas only two shifts predicted for the 1-Cl,2-OH structure agree with those observed. Three chemical shifts are definitive in es-

Table VI. Observed and Predicted ^{13}C Chemical Shifts for a Dichloronaphthol Metabolite of 2,6-Dichloronaphthalene

	δ_C observed	δ_C predicted for 2,6-Cl_2,1-OH	δ_C predicted for 1,6-Cl_2,2-OH	Deviations from mean predicted values, ppm: 2,6-Cl_2,1-OH	Deviations from mean predicted values, ppm: 1,6-Cl_2,2-OH
Quaternary carbons	149.67	147.19–149.90	148.96–154.12	0.42	−2.67
	130.12	*131.58–133.55*	*130.12–131.77*	−2.90	−0.58
	130.06	*132.58–132.68*	*130.02–130.80*	−2.58	−0.40
	129.54	*123.09–125.21*	*127.77–130.79*	5.90	−0.21
	113.52	114.04–115.02	113.44–113.73	−1.24	−0.04
CH carbons	128.39	127.41–128.12	128.38–128.49	0.53	−0.03
	127.54	126.80–127.52	127.30–128.27	0.25	−0.32
	126.90	126.37–126.38	126.65–127.17	0.52	0.00
	124.59	*122.20–122.70*	*124.52–124.95*	2.25	−0.15
	118.51	*121.27–121.50*	*118.56–119.01*	−2.93	−0.34

tablishing the structure: those for the first and third quaternary carbons and that for the last (lowest frequency) protonated carbon.

Thus, without specific assignments of ^{13}C resonances, and despite the complications of steric and hydrogen bonding effects, the use of additive substituent parameters is effective in isomer identification.

The same technique was used to identify a metabolite of 2,6-dichloronaphthalene. The mass spectrum and the ^1H NMR spectrum showed the metabolite to be a dichloronaphthol but could not unambiguously indicate whether it was 2,6-dichloro-1-hydroxynaphthalene or 1,6-dichloro-2-hydroxynaphthalene.[2] A range for the ^{13}C chemical shift of each carbon in each of the two isomers was predicted. For the 1-hydroxyl isomer the predictions were based on the following: (a) naphthalene chemical shifts plus parameters from Table III; (b) 2,6-dichloronaphthalene chemical shifts plus 1-OH parameters from Table III; (c) 2-chloro-1-hydroxynaphthalene chemical shifts plus 6-Cl parameters from Table III; and (d) 2-chloronaphthalene chemical shifts plus 1-OH and 6-Cl parameters from Table III. For the 2-hydroxyl isomer predictions were made similarly using the chemical shifts of (e) naphthalene, (f) 1-chloro-2-hydroxynaphthalene, and (g) 1-chloronaphthalene, plus the appropriate substituent parameters from Table III.

The observed ^{13}C chemical shifts for the metabolite are compared with the additivity predictions in Table VI. The average deviation from the mean predicted chemical shift for each carbon is only 0.47 ppm for the 2-naphthol but 1.95 ppm for the 1-naphthol. All observed values lie in the predicted range for the 2-naphthol, whereas only two observed values lie therein for the 1-naphthol. If reasonable agreement between experimental and predicted chemical shifts is defined as the predicted range ±1 ppm, all shifts for the 2-naphthol are still in agreement with those predicted, but only five are so for the 1-napithol. Five chemical shifts are definitive: the second, third, and fourth for the quaternary carbons and the last two for the protonated carbons. Clearly, the metabolite is 1,6-dichloro-2-hydroxynaphthalene.

Naturally, one would expect that the more closely related the chosen model compound is to the compound of interest the better the agreement would be between the predicted and observed ^{13}C chemical shifts. This is indeed the case. The best agreement, with an average deviation of 0.50 ppm, is for (f), which includes the ortho chlorine hydroxyl interactions in the chemical shifts of the parent compound. But (e) works nearly as well, with an average deviation of 0.75 ppm; yet only the shifts of naphthalene itself, plus the appropriate substituent parameters, were used.

We have recently[32] used this method to identify a metabolite of 4,4′-dichlorobiphenyl as 3,4′-dichloro-4-hydroxybiphenyl rather than the expected isomer 4,4′-dichloro-3-hydroxybiphenyl. This identification was confirmed by comparison with a synthetic standard.

Thus, additivity works well and, in fact, far better than expected in systems where steric and hydrogen bonding interactions cause deviations from predicted ^{13}C chemical shifts. Despite these deviations, unambiguous characterization of similar isomers can be accomplished.

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